Long-Term Outcomes Among Adult Survivors of Childhood Central Nervous System Malignancies in the Childhood Cancer Survivor Study

Gregory T. Armstrong, Qi Liu, Yutaka Yasui, Sujuan Huang, Kirsten K. Ness, Wendy Leisenring, Melissa M. Hudson, Sarah S. Donaldson, Allison A. King, Marilyn Stovall, Kevin R. Krull, Leslie L. Robison, Roger J. Packer

Background Adult survivors of childhood central nervous system (CNS) malignancies are at high risk for long-term morbidity and late mortality. However, patterns of late mortality, the long-term risks of subsequent neoplasms and debilitating medical conditions, and sociodemographic outcomes have not been comprehensively characterized for individual diagnostic and treatment groups.

Methods We collected information on treatment, mortality, chronic medical conditions, and neurocognitive functioning of adult 5-year survivors of CNS malignancies diagnosed between 1970 and 1986 within the Childhood Cancer Survivor Study. Using competing risk framework, we calculated cumulative mortality according to cause of death and cumulative incidence of subsequent neoplasms according to exposure and dose of cranial radiation therapy (RT). Neurocognitive impairment and socioeconomic outcomes were assessed with respect to dose of CNS radiotherapy to specific brain regions. Cumulative incidence of chronic medical conditions was compared between survivors and siblings using Cox regression models. All tests of statistical significance were two-sided.

Results Among all eligible 5-year survivors (n = 2821), cumulative late mortality at 30 years was 25.8% (95% confidence interval [CI] = 23.4% to 28.3%), due primarily to recurrence and/or progression of primary disease. Patients who received cranial RT of 50 Gy or more (n = 813) had a cumulative incidence of a subsequent neoplasm within the CNS of 7.1% (95% CI = 4.5% to 9.6%) at 25 years from diagnosis compared with 1.0% (95% CI = 0% to 2.3%) for patients who had no RT. Survivors had higher risk than siblings of developing new endocrine, neurological, or sensory complications 5 or more years after diagnosis. Neurocognitive impairment was high and proportional to radiation dose for specific tumor types. There was a dose-dependent association between RT to the frontal and/or temporal lobes and lower rates of employment, and marriage.

Conclusions Survivors of childhood CNS malignancies are at high risk for late mortality and for developing subsequent neoplasms and chronic medical conditions. Care providers should be informed of these risks so they can provide risk-directed care and develop screening guidelines.

J Natl Cancer Inst 2009;101:946–958

Modern therapy for children with central nervous system (CNS) malignancies often includes both surgical resection and a combination of CNS-directed radiation therapy (RT) and chemotherapy. With this multimodal approach, 74% of children younger than 20 years and diagnosed with a CNS malignancy become 5-year survivors (1). However, increased exposure to multimodal therapy may increase the risk of long-term morbidity and late mortality.

Among survivors of primary pediatric cancers, survivors of CNS malignancies are at the highest risk for late mortality (2–4). However, patterns of cause-specific late mortality (eg, rates of recurrence-related vs treatment-related death) have not been

Affiliations of authors: Department of Epidemiology and Cancer Control and Department of Oncology, St Jude Children's Research Hospital, Memphis, TN (GTA, KKN, MMH, KRK, LLR, SH); Department of Public Health Sciences, University of Alberta, Edmonton, AB (QL, YY); Department of Clinical Statistics and Cancer Prevention, Fred Hutchinson Cancer Research Center, Seattle, WA (WL); Department of Radiation Oncology, Stanford University Medical Center, Stanford, CA (SSD); Program in Occupational Therapy and Department of Pediatrics, Washington University, St Louis, MO (AAK); Department of Radiation Physics, University of Texas, M. D. Anderson Cancer Center, Houston, TX (MS); Department of Pediatrics and Department of Neurology, Brain Tumor Institute, Children's National Medical Center and George Washington University, Washington, DC (RJP).

Correspondence to: Gregory T. Armstrong, MD, MSCE, Department of Epidemiology and Cancer Control, St Jude Children's Research Hospital, 262 Danny Thomas Place, Mail Stop 735, Memphis, TN 38105 (e-mail: greg.armstrong@stjude.org).

See "Funding" and "Note" following "References."

DOI: 10.1093/jnci/djp148

detailed within individual CNS diagnostic groups. Furthermore, survivors of CNS malignancies are at risk for developing subsequent neoplasms and debilitating chronic medical conditions (5–15), but the incidence of and risk factors for these conditions in the second, third, and fourth decades of survival are not well documented. Finally, long-term survivors of CNS cancer are at high risk for neurocognitive impairment, which may adversely impact sociodemographic outcomes (16,17).

Using the unique resource of the Childhood Cancer Survivor Study (CCSS), we have comprehensively assessed the long-term survivorship experience of 1887 adult survivors of childhood CNS tumors who were diagnosed and treated between 1970 and 1986. Previous reports from the CCSS have presented limited results for CNS survivors in this retrospective cohort (5,13–15,18–20). This study is intended to analyze these individuals in greater depth and is based on updated data on long-term outcomes. The results of this analysis may provide a benchmark for assessment of patients in future treatment eras.

CONTEXT AND CAVEATS

Prior knowledge

The long-term health of those treated as children for malignancies of the central nervous system (CNS) had been incompletely characterized.

Study design

Retrospective cohort study relying on a questionnaire, medical records, and the National Death Index for information. Siblings were selected randomly to serve as control subjects where appropriate. Cumulative mortality and incidence of subsequent neoplasms were analyzed using competing risk models.

Contribution

This study provided a comprehensive assessment of the long-term risks of mortality, subsequent medical complications, and neurocognitive impairment in survivors of pediatric malignancies of the CNS, and how radioactive treatment was associated with these risks.

Implications

Due to high risks of mortality, subsequent cancers, and other medical conditions, survivors of CNS malignancies will need specialized care and screening.

Limitations

Treatment of pediatric cancers has changed considerably since the time when the patients in this cohort were treated; the results of this analysis may not be applicable to future survivors.

From the Editors

Methods

The CCSS

The CCSS is a retrospective cohort of children and adolescents treated for cancer at 26 collaborating institutions in the United States and Canada (Supplementary Appendix, available online). Eligibility criteria included diagnosis of childhood cancer before age 21 years, initial treatment between January 1, 1970, and December 31, 1986, and survival for at least 5 years after diagnosis. The cohort and study design have been previously described (21). Respective institutional review boards of participating centers reviewed and approved the CCSS protocol.

Beginning in 1994, participants completed a self-administered baseline questionnaire or telephone interview providing demographic and health-related outcomes information. Parents completed the baseline questionnaire for participants younger than 18 years, and for participants older than 18 years who were unable to complete the questionnaire themselves. Rates of parental completion for living adult (ie, >18 years of age) CNS tumor survivors (3.7%) were similar to rates for survivors of other pediatric cancers (3.1%). Subsequent update questionnaires and interviews were administered every 2–3 years (all study surveys are available at www.stjude.org/ccss). Treatment information (on surgical procedures, chemotherapy, and RT) was abstracted from medical records using a structured protocol. Records from radiation oncology departments were centrally reviewed to quantify radiation exposure to the frontal, temporal, and occipital lobes of the brain and posterior fossa with maximum radiation dose estimated for each region (14) based on measurements in a tissue-equivalent phantom and a three-dimensional computer model of the patient. The dosimetry method has been previously described (22).

Study Population

Of the 20691 participants eligible for the CCSS cohort, 2888 (14.0%) were survivors of CNS malignancies. International Classification of Diseases for Oncology-2 codes used to classify members of the cohort are listed in Supplementary Table 1 (available online) (23). Of the survivors of CNS malignancies, 491 (17.0%) could not be located, 511 (17.7%) declined participation, and 9 (0.3%) could not participate because of language barriers, leaving 1877 participants in the study. For this analysis, participants and nonparticipants were similar in terms of sex, cancer diagnosis, and age at diagnosis (21,24). Late mortality was assessed in 2821 of the 2888 eligible survivors of CNS malignancy rather than in only the 1877 participants because study participation was not required. Vital status was ascertained by the US National Death Index (NDI) and, for Canadian survivors, by CCSS surveys (except for 67 Canadian survivors who did not participate in the CCSS surveys). Subsequent neoplasms and chronic medical conditions were assessed in the 1877 participants who completed the baseline questionnaire. Sociodemographic factors and health status were studied in 1033 and 1001 participants, respectively, who were older than 25 years at the time of the second follow-up study of the cohort. The CCSS–Neurocognitive Questionnaire (CCSS-NCQ), a reliable and valid measure of neurocognitive functioning in adult survivors of pediatric cancer (25), was completed by 802 participants.

Siblings of CCSS participants were selected, by simple random sampling of survivors with at least one sibling, to participate in a comparison population that was neither diagnosed nor treated for cancer. If a participant had multiple siblings, the sibling closest in age to the participant was recruited. Of 4782 siblings selected, 3899 (81.5%) participated in the CCSS. Four hundred and ninety-six of 1877 CNS patients had a sibling control.

Table 1. Demographics of survivors of central nervous system malignancies and their siblings*

Characteristic	CNS survivors, No. (%) (n = 1877)	Siblings, No. (%) (n = 3899)	*P*
Sex of patient			<.001
Male	1034 (55.1)	1875 (48.1)	
Female	843 (44.9)	2024 (51.9)	
Age at baseline questionnaire, y			<.001
0–14	252 (13.4)	431 (11.1)	
15–19	374 (19.9)	655 (16.8)	
20–24	442 (23.5)	673 (17.3)	
25–29	404 (21.5)	708 (18.2)	
30–34	275 (14.7)	655 (16.8)	
≥35	130 (6.9)	777 (19.9)	
Race/ethnicity			<.001
White, non-Hispanic	1611 (86.1)	3414 (90.7)	
Black, non-Hispanic	76 (4.1)	103 (2.7)	
Hispanic/Latino	68 (3.6)	138 (3.7)	
Other	116 (6.2)	107 (2.8)	
CNS type			
Astrocytoma/glial tumor	1233 (65.7)		
Medulloblastoma/PNET	395 (21.0)		
Ependymoma	148 (7.9)		
Other CNS tumors	101 (5.4)		
Age at diagnosis, y			
0–3	500 (26.6)		
4–9	699 (37.2)		
10–14	462 (24.6)		
15–20	216 (11.5)		
Treatment†			
Surgery only	431 (26.0)		
Surgery + RT	689 (41.6)		
Surgery + RT + chemo	447 (27.0)		
Other	88 (5.3)		
Cranial RT dose			
None	483 (30.8)		
>0 to <50 Gy	272 (17.3)		
≥50 Gy	813 (51.8)		
RT location†‡			
Cranial + spinal RT	410 (26.2)		
Cranial RT, no spinal RT	674 (43.0)		
No cranial or spinal RT	483 (30.8)		
Combined modality treatment‡			
Surgery only	431 (29.0)		
Surgery + CRT >0 to <50 Gy, no chemo	170 (11.5)		
Surgery + CRT ≥50 Gy, no chemo	466 (31.4)		
Surgery + CRT >0 to <50 Gy + chemo	93 (6.3)		
Surgery + CRT ≥50 Gy + chemo	324 (21.8)		

* PNET = primitive neuroectodermal tumor; RT = radiotherapy; CRT = cranial radiotherapy; chemo = chemotherapy; CNS = central nervous system.

† Percentages based on available data.

‡ Spinal irradiation does not include patients who received total body irradiation.

Statistical Analysis

Descriptive data on demographic (sex of patient, age at baseline questionnaire, race, ethnicity, CNS subtype, and age at diagnosis) and treatment characteristics (surgery, radiation, and chemotherapy treatment, cranial RT dose, RT region, and combined modality treatment) were summarized for the 1877 survivors and, where appropriate, compared with those of the 3899 randomly selected siblings. Age- and sex-adjusted comparisons were also made between survivors and siblings for educational attainment, employment, income, marital status, and health status, using generalized estimating equations to account for potential within-family correlation (26).

To assess late mortality, person-years at risk were computed from the time of cohort entry to date of death or censoring. US participants were censored on December 31, 2002, the cutoff date of the most recent NDI search; Canadian survivors were censored on either December 31, 2002, or the date of last survey. Cumulative curves were compared using the method proposed by Gray (27). Groups that were compared with respect to cumulative mortality were divided according to sex or CNS subtypes (astrocytoma and glial tumors, ependymoma, or medulloblastoma and primitive neuroectodermal tumors).

Methods used in this study for calculating standardized mortality ratios (SMRs) and exact 95% confidence intervals (CIs) have

been reported previously (2,20). The covariates used in the mortality analysis were sex; age at diagnosis (0–3, 4–9, 10–14, and 15–20 years old); calendar year of diagnosis (1970–1973, 1974–1977, 1978–1981, and 1982–1986); years since diagnosis (5–9, 10–14, 15–19, 20–24, 25–29, and 30–34 years); CNS subtypes (astrocytoma and glial tumors, ependymoma, and medulloblastoma and primitive neuroectodermal tumors); treatment modality (surgery alone, surgery and RT, and surgery and RT with chemotherapy); cranial RT dose (no exposure, <50 Gy, and ≥50 Gy); RT region (cranial RT and no spinal RT, cranial RT and spinal RT, and neither cranial RT nor spinal RT); and treatment modality and cranial RT dose (surgery alone, surgery and cranial RT <50 Gy and no chemotherapy, surgery and cranial RT ≥50 Gy and no chemotherapy, surgery and cranial RT <50 Gy and chemotherapy, or surgery and cranial RT ≥50 Gy and chemotherapy) with doses more than 50 Gy representing high-dose RT exposure.

To assess the occurrence of subsequent neoplasms among survivors, cumulative incidence was estimated using death as a competing risk (28). Subsequent neoplasms occurring before cohort entry were included as prevalent cases at cohort entry. The cumulative incidence of subsequent neoplasms was compared according to the dose of cranial RT (no exposure, <50 Gy, and ≥50 Gy). Standardized incidence ratios (SIRs) for the occurrence of subsequent malignant neoplasms and specific types of subsequent malignant neoplasms were calculated using the US Surveillance, Epidemiology, and End Results cancer incidences as reference rates (29).

The occurrence and severity of chronic medical conditions were determined as described previously (13). We used log-binomial regression to estimate a prevalence ratio for each chronic condition, comparing CNS survivors and CCSS siblings, adjusting for age at enrollment (5–9, 10–14, ≥15 years), sex, and race/ethnic group (white vs nonwhite) (30). Modifications of a log-binomial model with generalized estimating equations were used to account for potential within-family correlation (31). The incidence of new chronic medical conditions after cohort entry (beyond 5 years of diagnosis) was assessed by Cox regression to estimate hazard ratios (HRs) comparing CNS survivors and CCSS siblings, adjusting for age at enrollment, sex, and race/ethnic group. The proportionality assumption of hazard functions was assessed graphically. Within-family correlations were accounted for by using sandwich SE estimates (32).

The proportion of survivors who scored below the corresponding 10th percentile of the sibling comparison group was calculated for each of the four subscales of the CCSS-NCQ. These were calculated with 95% confidence intervals according to cranial RT dose and CNS subtype. Confidence intervals for proportions were calculated with exact methods (33). Age- and sex-adjusted proportions were calculated and compared between the survivors and the siblings with respect to college graduation, employment, marriage, annual household income greater than $20 000, health insurance, and health status outcomes in log-binomial models (34). Among survivors, the impacts of cranial RT dose and RT region on these outcomes were evaluated in log-binomial models using the copy method and adjusted for sex, age at diagnosis, and the maximum radiation dose to any of the other three segments (35).

In all analyses, treatment exposures within the first 5 years of the original CNS cancer diagnosis were considered. Statistical analyses were performed using SAS Version 9.1 (SAS Institute, Inc, Cary, NC) and R 2.5.1, and all statistical inferences were based on two-sided tests.

Results

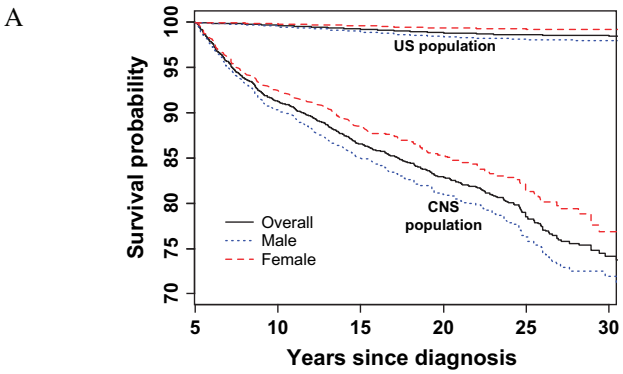
Characteristics of Participants Who Completed the Baseline Questionnaire

The median age at diagnosis of the 1877 participants who completed the baseline questionnaire was 7.5 years (range 0–20 years, Table 1); 1034 (55%) were male. Astrocytoma and glial tumors were the most common primary tumors. Most patients underwent surgery followed by RT (n = 689 [41.6%]) or RT and chemotherapy (n = 447 [27%]); 431 (26%) underwent surgery alone. Among the 1569 patients who received RT, 813 (51.8%) were exposed to cranial RT of 50 Gy or more to at least one brain region and (36.8%) received spinal RT.

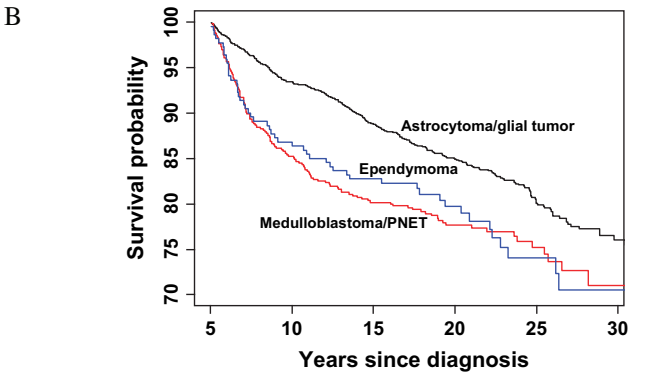
Overall and Cause-Specific Mortality

For the 2821 five-year survivors in whom late mortality was assessed, there were 43 369 person-years of follow-up and 546 deaths (13.8%). Cumulative all-cause mortality rates were 13.5%, 17.1%, 21.5%, and 25.8% at 15, 20, 25, and 30 years, respectively (Figure 1, A); males had greater risk of death than females (28.1% vs 23.1% at 30 years; $P < .001$). All-cause mortality at 30 years was higher in 5-year survivors of ependymoma (29.5%) and medulloblastoma (29.0%) than in 5-year survivors of astrocytoma and glial tumors (23.9%; $P < .001$ for both comparisons) (Figure 1, B).

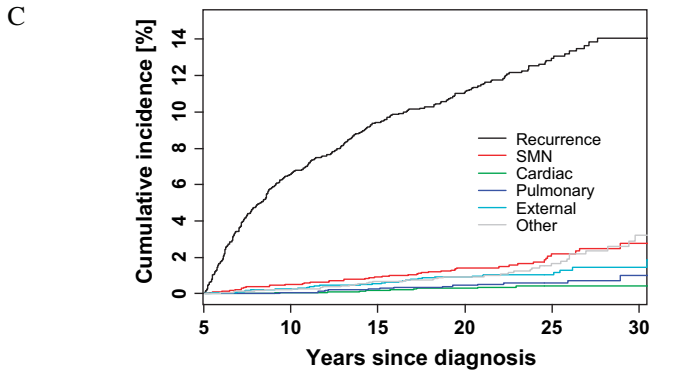
Compared with the US population, risk of death increased 13-fold for survivors of CNS malignancies (SMR = 12.9, 95% CI = 11.8 to 14.0); survivors of medulloblastoma and primitive neuroectodermal tumors were at highest risk (SMR = 17.4, 95% CI = 14.6 to 20.6) (Table 2). Recurrence and/or progression of primary disease was the most common cause of death (61%), followed by medical causes of death (21%) that included death attributable to subsequent neoplasms (9%), cardiac disease (3%), and pulmonary disease (3%). Cumulative cause-specific mortality at 30 years (Figure 1, C) was highest for primary cancer progression or recurrence (14%), followed by subsequent malignant neoplasm (2.8%), pulmonary disease (1.0%), and cardiac disease (0.4%). Annual death rates were highest for recurrence or progression of primary malignancy in the 5–30 years after diagnosis, after which death rates due to subsequent malignant neoplasms exceeded those for recurrence or progression (data not shown). Although this pattern of late recurrence or progression is expected for survivors with gliomas, even for survivors of ependymoma and medulloblastoma, the death rate from second malignant neoplasms did not exceed the rate of death due to recurrence until >20 years from diagnosis. Cumulative mortality due to recurrence was higher in males than in females (15.6% vs 12.1% at 30 years, $P = .05$) (Figure 1, D). Mortality from nonrecurrent, nonprogressive disease increased 25–30 years after diagnosis with statistically significantly increased risks of death due to subsequent malignant neoplasms (SMR = 13.9, 95% CI = 10.4 to



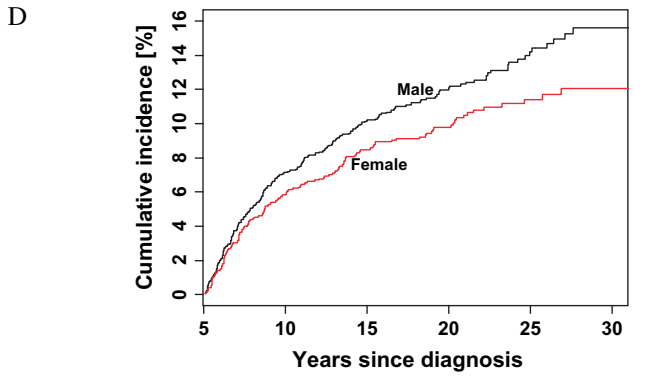
Patients at risk:						
Overall	2821	2574	2430	1414	663	204
Male	1568	1415	1325	775	357	112
Female	1253	1159	1105	639	306	92
Survival probability, % (95% CI):						
Overall	100 (100 to 100)	91.3 (90.2 to 92.3)	86.5 (85.3 to 87.8)	82.9 (81.5 to 84.3)	78.5 (76.7 to 80.3)	74.2 (71.7 to 76.6)
Male	100 (100 to 100)	90.3 (88.8 to 91.8)	85.0 (83.2 to 86.8)	81.0 (79.0 to 83.0)	76.2 (73.7 to 78.8)	71.9 (68.7 to 75.2)
Female	100 (100 to 100)	92.5 (91.0 to 94.0)	88.4 (86.7 to 90.2)	85.3 (83.3 to 87.3)	81.3 (78.7 to 83.9)	76.9 (73.1 to 80.6)



Patients at risk:						
Astrocytoma/glial	1891	1767	1673	980	482	148
Medulloblastoma/PNET	572	489	460	274	116	33
Ependymoma	220	192	182	108	53	23
Survival probability, % (95% CI):						
Astrocytoma/glial	100 (100 to 100)	93.5 (92.4 to 94.6)	88.8 (87.4 to 90.2)	85.0 (83.3 to 86.6)	80.0 (77.8 to 82.2)	76.1 (73.2 to 79.0)
Medulloblastoma/PNET	100 (100 to 100)	85.3 (82.4 to 88.2)	80.6 (77.3 to 83.8)	78.1 (74.7 to 81.6)	75.8 (71.9 to 79.8)	71.0 (65.4 to 76.7)
Ependymoma	100 (100 to 100)	86.8 (82.3 to 91.3)	82.7 (77.7 to 87.7)	79.7 (74.3 to 85.2)	74.1 (67.4 to 80.8)	70.5 (62.5 to 78.5)



Patients at risk:	2821	2574	2430	1414	663	204
Cumulative Incidence, % (95% CI):						
Recurrence	0 (0 to 0)	6.6 (5.6 to 7.5)	9.4 (8.4 to 10.5)	11.1 (9.9 to 12.2)	13.0 (11.6 to 14.4)	14.0 (12.5 to 15.6)
SMN	0 (0 to 0)	0.5 (0.3 to 0.8)	0.9 (0.6 to 1.3)	1.4 (1.0 to 1.9)	2.2 (1.5 to 2.9)	2.8 (1.8 to 3.8)
Cardiac	0 (0 to 0)	0.1 (0.0 to 0.2)	0.2 (0.0 to 0.3)	0.3 (0.1 to 0.5)	0.4 (0.2 to 0.7)	0.4 (0.2 to 0.7)
Pulmonary	0 (0 to 0)	0.1 (0.0 to 0.2)	0.3 (0.1 to 0.5)	0.5 (0.2 to 0.7)	0.6 (0.3 to 0.9)	1.0 (0.3 to 1.7)
External	0 (0 to 0)	0.3 (0.1 to 0.5)	0.6 (0.3 to 0.8)	0.9 (0.6 to 1.3)	1.0 (0.6 to 1.4)	1.4 (0.8 to 2.0)
Other	0 (0 to 0)	0.1 (0.0 to 0.2)	0.5 (0.3 to 0.8)	0.8 (0.4 to 1.1)	1.5 (0.9 to 2.1)	3.1 (1.7 to 4.4)



Patients at risk:						
Male	1568	1415	1325	775	357	112
Female	1253	1159	1105	639	306	92
Cumulative Incidence, % (95% CI):						
Male	0 (0 to 0)	7.1 (5.9 to 8.4)	10.2 (8.7 to 11.7)	12.1 (10.4 to 13.7)	14.2 (12.2 to 16.2)	15.6 (13.3 to 17.9)
Female	0 (0 to 0)	5.8 (4.5 to 7.1)	8.5 (6.9 to 10.0)	9.8 (8.1 to 11.5)	11.4 (9.5 to 13.4)	12.1 (10.0 to 14.2)

Figure 1. Mortality experience of 5-year survivors of childhood central nervous system (CNS) malignancies. **A**) All-cause and sex-specific mortality among 5-year survivors of CNS malignancies compared with the age-adjusted US population. **B**) All-cause mortality by primary diagnosis. **C**) Cumulative cause-specific mortality. **D**) Cumulative mortality attributable to recurrence by sex. PNET = primitive neuroectodermal tumor, SMN = second malignant neoplasm.

18.3), cardiac disease (SMR = 4.2, 95% CI = 2.0 to 7.7), pulmonary disease (SMR = 17.1, 95% CI = 9.8 to 27.8), and deaths due to other causes (SMR = 3.9, 95% CI = 2.7 to 5.4).

Subsequent Neoplasms

The 1877 survivors evaluated for the occurrence of subsequent neoplasms accrued more than 27 550 person-years from time of entry into the CCSS cohort, with a median follow-up of 19.6 years (range = 5.1–34.6 years) from initial CNS cancer diagnosis. There were 255 confirmed subsequent neoplasms in 151 patients who had achieved 5-year survival status (Table 3). The cumulative incidence for all subsequent neoplasms in the cohort (Figure 2, A) was 10.7% (95% CI = 8.8% to 12.6%) at 25 years from diagnosis. Cumulative incidences for nonmelanoma skin cancer, benign meningiomas, and all other subsequent neoplasms (excluding nonmelanoma skin cancer and benign meningioma) were 2.9% (95% CI = 1.8 to 4.0), 3.3% (95% CI = 2.2 to 4.5), and 4.5% (95% CI = 3.3 to 5.7), respectively. Incidence of meningiomas increased sharply with continued follow-up (Figure 2, B), even among patients with no previous diagnosis of meningioma at 25 years (incidence was 3.5% at 30 years, 95% CI = 0.9 to 6.1). Maximum cranial RT dose received was associated with the

Table 2. Number of deaths and standardized mortality ratios among 5-year survivors of central nervous system tumors*

Variables	Analyzed cohort	Alive†	Dead†	SMR‡ (95% CI)	*P*§
Total no. of patients	2821	2275	546	12.9 (11.8 to 14.0)	
Sex					<.001
Male	1568	1230	338	10.6 (9.5 to 11.8)	
Female	1253	1045	208	19.6 (17.0 to 22.5)	
Age of diagnosis, y					<.001
0–3	758	595	163	17.2 (14.7 to 20.1)	
4–9	1052	873	179	15.0 (12.8 to 17.3)	
10–14	672	544	128	9.7 (8.1 to 11.6)	
15–20	339	263	76	9.7 (7.6 to 12.1)	
Year of diagnosis					.003
1970–1973	372	267	105	10.6 (8.7 to 12.9)	
1974–1977	518	372	146	14.2 (12.0 to 16.7)	
1978–1981	655	543	112	10.8 (8.9 to 13.0)	
1982–1986	1276	1093	183	15.4 (13.2 to 17.7)	
Survival after diagnosis, y					<.001
5–9	248	2	246	28.0 (24.7 to 31.8)	
10–14	144	10	134	11.7 (9.8 to 13.9)	
15–19	1017	933	84	7.4 (5.9 to 9.1)	
20–24	750	698	52	7.4 (5.6 to 9.7)	
25–29	459	434	25	7.7 (5.0 to 11.4)	
30–34	203	198	5	8.4 (2.7 to 19.6)	
Diagnosis					<.001
Astrocytoma/glial tumor	1891	1559	332	11.2 (10.1 to 12.5)	
Medulloblastoma/PNET	572	439	133	17.4 (14.6 to 20.6)	
Ependymoma	220	168	52	15.9 (11.9 to 20.9)	
Others	138	109	29	14.4 (9.6 to 20.7)	
Treatment type‖					<.001
Surgery alone	431	408	23	3.2 (2.0 to 4.8)	
Surgery + RT	689	596	93	7.9 (6.4 to 9.7)	
Surgery + RT + chemo	447	312	135	26.0 (21.8 to 30.7)	
Other	88	67	21	22.2 (13.7 to 34.0)	
Cranial RT dose‖					<.001
None	483	449	34	4.5 (3.1 to 6.3)	
>0 to <50 Gy	272	222	50	12.0 (8.9 to 15.8)	
≥50 Gy	813	645	168	14.0 (12.0 to 16.3)	
RT location‖					.28
CRT, no spinal RT	674	542	132	12.7 (11.8 to 18.3)	
CRT + spinal RT	410	325	85	14.8 (10.6 to 15.1)	
No CRT, no spinal RT	483	449	34	4.5 (3.1 to 6.3)	
Treatment and CRT‖					<.001
Surgery alone	431	408	23	3.2 (2.0 to 4.8)	
S + >0 to <50 Gy, no chemo	170	149	21	7.3 (4.5 to 11.2)	
S + ≥50 Gy, no chemo	466	403	63	7.9 (6.1 to 10.2)	
S + >0 to <50 Gy + chemo	93	66	27	24.1 (15.9 to 35.0)	
S + ≥50 Gy + chemo	324	227	97	26.0 (21.1 to 31.7)	

* RT = radiotherapy; CRT = cranial radiotherapy; S = surgery; CI = confidence interval; PNET = primitive neuroectodermal tumor; chemo = chemotherapy; SMR = standardized mortality ratio.

† As of December 31, 2002.

‡ Age and sex standardized according to National Center for Health Statistics criteria. All SMRs had $P < .01$ (assessed using the exact two-sided tests inverted from the corresponding exact Poisson two-sided CIs).

§ For comparison between groups.

‖ Restricted to patients with medical records abstracted; treatment data were cutoff at 5 years from diagnosis.

cumulative incidence of any subsequent neoplasm within the CNS (Figure 2, C). Patients receiving cranial RT of 50 or more Gy had a cumulative incidence of a CNS subsequent neoplasm 25 years after diagnosis of 7.1% (95% CI = 4.5 to 9.6) compared with 5.2% for those receiving more than 0 but less than 50 Gy (95% CI = 2.1 to 8.3) and 1.0% for no RT exposure (95% CI = 0 to 2.3). Excluding 112 nonmelanoma skin cancers, 59 benign meningiomas, and eight other benign lesions, 76 subsequent malignant neoplasms occurred in the 1877 survivors who were evaluated (Table 3). The overall SIR was 4.1 (95% CI = 3.2 to 5.2); the most common subsequent malignant neoplasms were CNS tumors (15 gliomas, four malignant meningiomas, one medulloblastoma or primitive neuroectodermal tumor; SIR = 25.3, 95% CI = 15.5 to 39.1), soft tissue sarcomas (SIR = 8.4, 95% CI = 3.6 to 16.5), and thyroid cancers (SIR = 11.2, 95% CI = 5.8 to 19.6). In general, CNS tumor survivors had higher rates of

Table 3. Standardized incidence ratios for occurrence of subsequent neoplasms in the 1877 survivors in the Childhood Cancer Survivor Study cohort*

Neoplasm	No. observed	No. expected	SIR (95% CI)	Median No. of years to occurrence
Subsequent neoplasms for which SIRs could be calculated	76	18.5	4.1 (3.2 to 5.2)	16.0
Leukemia	3	0.7	4.1 (0.8 to 12.0)	12.5
AML	2	0.2	8.0 (0.9 to 29.1)	18.8
Other leukemias	1	0.1	6.9 (0.1 to 38.6)	5.1
Lymphoma	3	1.9	1.5 (0.3 to 4.5)	14.4
CNS	20	0.7	25.3 (15.5 to 39.1)	14.0
Astrocytoma/glial tumors	15	0.6	24.3 (13.6 to 40.1)	14.0
Malignant menigiomas	4	0.0	714.7 (192.3 to 1829.7)	23.7
Medulloblastoma/PNET	1	0.1	13.1 (0.2 to 72.8)	14.0
Breast	4	1.4	2.8 (0.8 to 7.3)	26.6
Bone	5	0.3	15.1 (4.9 to 35.2)	8.2
Soft tissue sarcoma	8	1.0	8.4 (3.6 to 16.5)	12.6
Thyroid	12	1.1	11.2 (5.8 to 19.6)	17.5
Melanoma	5	1.7	2.9 (0.9 to 6.7)	15.7
All other cancers	16	9.3	1.7 (1.0 to 2.8)	17.5
Second neoplasms for which SIRs could not be calculated				
Nonmelanoma skin cancer	112	NA	NA	21.0
Nonmalignant menigiomas	59	NA	NA	18.8
Myxopapillary ependymoma	1	NA	NA	
Neurilemmoma	4	NA	NA	
Melanoma in situ	1	NA	NA	
All other tumors	2	NA	NA	

* CI = confidence interval; PNET = primitive neuroectodermal tumor; AML = acute myeloid leukemia; CNS = central nervous system; NA = not applicable; SIR = standardized incidence ratio.

subsequent CNS neoplasms and lower rates of subsequent breast cancers compared with CCSS participants who did not have a CNS primary malignancy.

Chronic Medical Conditions

Of the 1877 survivors who we evaluated, 82% reported having at least one chronic medical condition; after accounting for death and censoring, cumulative incidence at 25 years was 91.6%, and 38% of the survivors reporting a serious or life-threatening (grade 3–4) condition. We calculated prevalence ratios, comparing survivors with siblings for chronic medical conditions in the first 5 years after diagnosis, and hazard ratios for developing a new chronic condition after 5 years (Table 4). Of the 588 survivors having no chronic health conditions before the 5-year time point, 42.9% subsequently developed at least one. Survivors had a statistically significantly higher risk than siblings of developing new endocrine (HR = 19.8, 95% CI = 14.5 to 27.1), neurological (including seizures) (HR = 5.6, 95% CI = 4.8 to 6.7), or sensory (including hearing loss) (HR = 12.5, 95% CI = 8.9 to 17.6) health conditions beyond the 5-year time point.

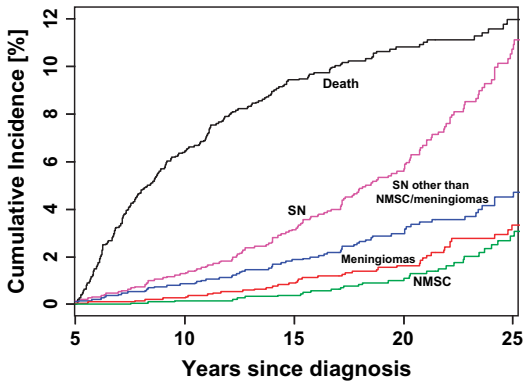
Neurocognitive Functioning

Compared with siblings, rates of neurocognitive impairment (a score below the 10th percentile of the sibling group's scores) were higher in all CNS survivor diagnostic groups after treatment with radiation (Table 5). Greater than 40% of medulloblastoma or primitive neuroectodermal tumor survivors had impaired attention and/or processing speed function; fewer displayed problems in organizational skills and emotional regulation. No clear dose–response relationship between cranial RT and impairment in attention and/or processing speed, emotional regulation, or organization was evident for patients with medulloblastoma or primitive neuroectodermal tumors. Survivors diagnosed with astrocytoma and glial tumors were impaired in attention and/or processing speed and memory by a statistically significant extent, with a clear cranial RT dose–response pattern. Survivors of astrocytoma and glial tumors exposed to higher doses of cranial radiotherapy also had a statistically significant increase in problems with organization and emotional regulation.

Sociodemographic Outcomes and Health Status

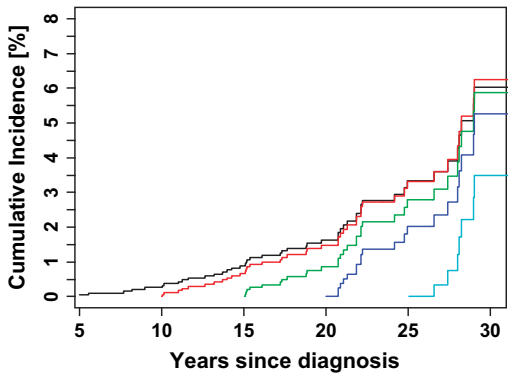
CNS survivors reported statistically significantly lower rates than siblings for all sociodemographic outcomes except lack of health insurance. After controlling for age, sex, and race and/or ethnicity, siblings were more likely than survivors to report current employment (RR = 1.4, 95% CI = 1.3 to 1.5), an income greater than $20 000 (RR = 1.2, 95% CI = 1.1 to 1.3), marriage (RR = 2.0, 95% CI = 1.8 to 2.2), and college graduation (RR = 1.4, 95% CI = 1.3 to 1.5). Region-specific dosimetry analyses controlling for age at diagnosis, sex, and maximum RT dose to other regions showed that exposure of the temporal or frontal lobe to 50 Gy or more was independently and statistically significantly associated with higher risk of unemployment (RR = 1.7, 95% CI = 1.1 to 2.6 and RR = 2.1, 95% CI = 1.1 to 4.1, respectively) and that radiation to any

A



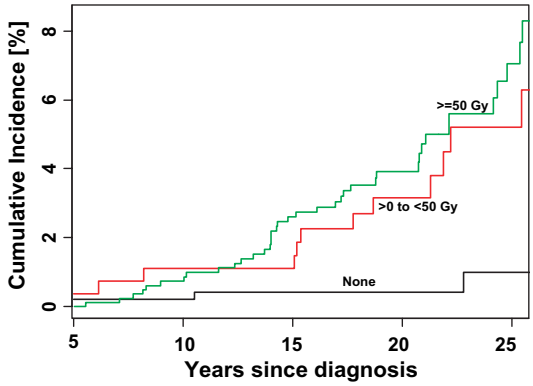
Patients at risk:	1877	1706	1479	885	397
Cumulative Incidence, % (95% CI):					
Death	0 (0 to 0)	6.4 (5.3 - 7.5)	9.4 (8.1 - 10.8)	10.8 (9.4 - 12.3)	12.0 (10.3 - 13.6)
SN	0 (0 to 0)	1.3 (0.8 - 1.8)	3.1 (2.3 - 4.0)	5.6 (4.5 - 6.7)	10.7 (8.8 - 12.6)
SN other than NMSC/meningiomas	0 (0 to 0)	0.9 (0.4 - 1.3)	1.9 (1.2 - 2.5)	3.0 (2.1 - 3.8)	4.5 (3.3 - 5.7)
Meningiomas	0 (0 to 0)	0.3 (0.0 - 0.5)	0.9 (0.5 - 1.3)	1.6 (1.0 - 2.3)	3.3 (2.2 - 4.5)
NMSC	0 (0 to 0)	0.2 (0.0 - 0.3)	0.4 (0.1 - 0.7)	1.0 (0.5 - 1.5)	2.9 (1.8 - 4.0)

B



Patients at risk:	1877	1706	1479	885	397	110
Cumulative Incidence, % (95% CI), Conditioned on Meningioma-free Survival At:						
5 years	0 (0 to 0)	0.3 (0.0 - 0.5)	0.9 (0.5 - 1.3)	1.6 (1.0 - 2.3)	3.3 (2.2 - 4.5)	6.0 (3.8 - 8.3)
10 years		0 (0 to 0)	0.7 (0.3 - 1.1)	1.5 (0.9 - 2.1)	3.3 (2.1 - 4.5)	6.2 (3.8 - 8.7)
15 years			0 (0 to 0)	0.9 (0.3 - 1.4)	2.8 (1.6 - 4.0)	5.9 (3.3 - 8.5)
20 years				0 (0 to 0)	2.0 (0.9 - 3.2)	5.3 (2.6 - 7.9)
25 years					0 (0 to 0)	3.5 (0.9 - 6.1)

C



Patients at risk:					
None	483	461	412	241	127
<50 Gy	272	246	228	157	82
>=50 Gy	813	719	615	354	143
Cumulative Incidence, % (95% CI):					
None	0 (0 to 0)	0.2 (0.0 - 0.6)	0.4 (0.0 - 1.0)	0.4 (0.0 - 1.0)	1.0 (0.0 - 2.3)
<50 Gy	0 (0 to 0)	1.1 (0.0 - 2.3)	1.1 (0.0 - 2.3)	3.2 (1.0 - 5.3)	5.2 (2.1 - 8.3)
>=50 Gy	0 (0 to 0)	0.7 (0.2 - 1.3)	2.6 (1.5 - 3.7)	3.9 (2.5 - 5.4)	7.1 (4.5 - 9.6)

Figure 2. Subsequent neoplasms in 5-year survivors of central nervous system (CNS) malignancies. **A**) Cumulative incidence of subsequent neoplasms (SN) with death as competing risk. **B**) Cumulative incidence of detected meningioma conditioned on meningioma-free survival at 5, 10, 15, 20, and 25 years. **C**) Cumulative incidence of CNS second neoplasms by cranial radiation therapy dose. NMSC = nonmelanoma skin cancer.

region was associated with never being married. Radiation of 30–49 Gy and radiation more than 50 Gy to the temporal lobe, and radiation 50 Gy or more to the posterior fossa were independently associated with an annual household income of $20 000 or less (RR = 2.3, 95% CI = 1.3 to 4.3, RR = 2.9, 95% CI = 1.7 to 5.0, and RR = 2.1, 95% CI = 1.1 to 4.0, respectively) (Table 6).

CNS survivors reported higher rates of impaired health status than siblings in terms of general health (RR = 19.1, 95% CI = 13.0 to 27.9), mental health (RR = 1.5, 95% CI = 1.2 to 1.7), functional impairment (RR = 19.5, 95% CI = 14.9 to 25.4), activity limitations (RR = 36.2, 95% CI = 22.1 to 59.3), pain (RR = 7.9, 95% CI = 5.5 to 11.5), and cancer-related anxiety (RR = 9.7, 95% CI = 6.1 to 15.3). CNS survivors were 3.1 times (95% CI = 2.8 to 3.4) more likely than siblings to report at least one adverse health outcome.

Discussion

We have comprehensively assessed long-term outcomes of 5-year survivors of CNS tumors who were diagnosed and treated from 1970 to 1986. This extended follow-up evaluation of the CCSS cohort quantifies the occurrence and impact of late effects secondary to childhood CNS malignancies and their treatment on the

Table 4. Age-, sex-, and race-adjusted prevalence and hazard ratios of chronic health conditions among 5-year survivors of central nervous system tumors compared with sibling cohort*

Condition	PR† (95% CI)	HR (95% CI)‡
Any condition	29.5 (23.8 to 36.6)	6.4 (5.4 to 7.5)
Endocrine complications	49.1 (27.6 to 87.2)	19.8 (14.5 to 27.1)
Medication needed to initiate puberty	28.0 (6.7 to 117.8)	146.9 (35.4 to 608.8)
Growth hormone deficiency	400.7 (56.2 to 2856.9)	140.4 (51.3 to 384.1)
Growth hormone injections	267.6 (37.4 to 1912.5)	219.1 (54.5 to 880.5)
Hypothyroidism	31.4 (16.0 to 61.6)	13.0 (9.2 to 18.3)
Neurological complications	37.1 (28.3 to 48.7)	5.6 (4.8 to 6.7)
Weakness in arms or legs	82.9 (41.2 to 166.9)	12.2 (9.1 to 16.3)
Decreased sense of touch, feelings in hands, fingers, arms, or legs	45.7 (23.4 to 89.0)	3.9 (3.0 to 5.1)
Prolonged pain or abnormal sensations in arms, legs, or back	11.9 (6.6 to 21.3)	2.4 (1.9 to 3.0)
Problems with balance	102.7 (59.5 to 177.4)	18.0 (13.4 to 24.1)
Seizures	30.8 (19.4 to 48.9)	15.1 (10.7 to 21.2)
Tremor or movement problems	75.2 (35.5 to 159.2)	15.0 (10.1 to 22.4)
Paralysis	73.9 (32.9 to 166.2)	10.9 (6.9 to 17.3)
Sensory complications	35.3 (22.3 to 55.9)	12.5 (8.9 to 17.6)
Cataract	35.2 (4.7 to 264.5)	9.9 (5.1 to 19.3)
Hearing loss/deafness	20.2 (10.9 to 37.5)	21.0 (12.9 to 34.2)
Blindness	65.7 (31.0 to 139.2)	7.5 (4.1 to 13.5)

* All prevalence and rate ratios were statistically significant at a threshold of $\alpha = .001$ (calculated using two-sided Wald tests in Cox regression with robust SE estimates). PR = prevalence ratio; CI = confidence interval; HRs = hazard ratios.

† Prevalence ratio of conditions occurring in the first 5 years from diagnosis.

‡ Hazard ratio of a new condition beyond the 5-year time point among those with no previous condition.

lives of adult survivors. Unfortunately, survivors of CNS malignancies are at increased risk for mortality, subsequent cancer, and other outcomes resulting from their disease and treatment throughout their lifetime (36,37). Survival beyond 5 years of cancer diagnosis is often the benchmark for defining cancer survivorship. However, according to our analysis, even after surviving to the 5-year time point, more than 25% of CNS survivors will die within 30 years of their diagnosis. This mortality rate is 13 times higher than that for the age- and sex-matched US population. Late mortality is highest for 5-year survivors of ependymoma or embryonal tumors (approximately 33% of these patients die within 20 years). Survivors of medulloblastoma or primitive neuroectodermal tumors have a risk of death that is 17-fold that of the general population.

The annual death rate from second neoplasms did not surpass the annual death rate attributable to recurrence or progression of primary disease until approximately 30 years from diagnosis. This is much later than for other pediatric cancers, largely because low-grade gliomas in children may remain indolent for many years before ultimate progression and mortality (3,4,20,38–42). However, a similar pattern of late mortality was seen for medulloblastoma or primitive neuroectodermal tumors such that recurrence or progression of the original diagnosis was the primary cause of death until 20 years from diagnosis, and for ependymoma, recurrence or progression was the leading cause of death until 30 years after diagnosis. This pattern of late recurrence suggests a need for continued surveillance of disease well beyond the first 5 years from diagnosis.

Survivors of CNS tumors are at a statistically significantly increased risk of developing subsequent neoplasms, the most common site being the CNS. Previous investigations have reported cumulative incidence estimates of subsequent neoplasms for brain tumor survivors from single institutions (4% at 15 years) (6,7), cooperative groups (11% at 8 years) (8), and those covered in tumor registry–based studies (2.6% at 20 years; 7.3% at 30 years) (9–12), but these studies were limited by small sample size, inability to capture all second neoplasms, or insufficient treatment information.

Medical complications in survivors of pediatric CNS malignancies in the first 5 years subsequent to diagnosis are common due to neurosurgical procedures, therapeutic modalities, and the tumor itself (43). Unfortunately, even after 5 years, these survivors remain at high risk for developing new medical conditions. Many of the centers where childhood cancer patients are treated are pediatric-based institutions that are not able to provide continuing medical care for survivors of CNS neoplasms as they become adults. With increasing time from the original cancer diagnosis, the proportion of adult survivors of childhood cancer who receive long-term, risk-based follow-up in a cancer center or a clinic specific for long-term follow-up of cancer patients decreases substantially (44,45). Thus, disseminating information about risks to the general practitioners who follow-up the majority of survivors and developing guidelines for long-term care is important (46).

Previous investigations have established that CNS tumor survivors differ from those with other primary cancers in having more adverse outcomes in terms of education, employment, and health status and quality of life (47–54). However, most previous studies of the long-term effects of CNS neoplasms analyzed fewer than 100 CNS tumor survivors and followed them up for only the first 10 years of diagnosis, thus failing to capture outcomes in adulthood. We have previously reported statistically significant health impairment and poor sociodemographic outcomes in this population (55–57). In this study, we have identified important associations

Table 5. Neurocognitive outcomes in central nervous system tumor survivors by central nervous system subtype and cranial radiotherapy dose*

	Astrocytoma/glial tumors					Medulloblastoma/PNET					Ependymoma				
Cognitive domain†	N	Mean Score	95% CI	%Impaired†	95% CI	N	Mean Score	95% CI	%Impaired†	95% CI	N	Mean Score	95% CI	%Impaired‡	95% CI
Attention/processing speed															
No CRT	228	13.9	13.3 to 14.5	31.6	25.6 to 37.6	5	16.0	9.1 to 22.9	40.0	5.3 to 85.3	9	10.8	8.5 to 13.0	11.1	0.3 to 48.2
>0 to 50 Gy CRT	70	16.3	15.0 to 17.6	48.6	36.9 to 60.3	30	17.1	15.3 to 18.9	73.3	57.5 to 89.1	14	15.1	11.9 to 18.3	42.9	17.7 to 71.1
>50 Gy CRT	190	16.6	15.8 to 17.3	53.7	46.6 to 60.8	117	16.3	15.4 to 17.2	52.1	43.0 to 61.2	29	16.8	15.1 to 18.5	58.6	38.9 to 76.5
Emotional regulation															
No CRT	228	5.3	5.1 to 5.5	10.5	6.5 to 14.5	5	5.8	3.4 to 8.2	20.0	0.5 to 71.6	9	4.3	3.2 to 5.5	0.0	0.0 to 33.6
>0 to 50 Gy CRT	70	5.4	5.0 to 5.8	12.9	5.0 to 20.8	30	5.9	5.1 to 6.7	33.3	16.4 to 50.2	14	5.1	4.0 to 6.3	14.3	1.8 to 42.8
>50 Gy CRT	190	5.7	5.5 to 6.0	20.0	14.3 to 25.7	117	5.5	5.2 to 5.8	12.8	6.7 to 18.9	29	5.6	4.9 to 6.2	17.2	5.8 to 35.8
Organization															
No CRT	228	4.8	4.5 to 5.0	14.0	9.5 to 18.5	5	5.6	2.9 to 8.3	20.0	0.5 to 71.6	9	3.4	2.7 to 4.2	0.0	0.0 to 33.6
>0 to 50 Gy CRT	70	4.9	4.4 to 5.3	20.0	10.6 to 29.4	30	4.5	3.8 to 5.3	16.7	3.4 to 30.0	14	4.0	3.4 to 4.6	0.0	0.0 to 23.2
>50 Gy CRT	190	5.3	5.0 to 5.6	26.3	20.0 to 32.6	117	4.8	4.5 to 5.1	18.0	11.0 to 25.0	29	4.7	4.2 to 5.2	10.3	2.2 to 27.4
Memory															
No CRT	228	6.2	6.0 to 6.5	15.8	11.1 to 20.5	5	6.0	4.0 to 8.0	0.0	0.0 to 52.2	9	4.9	3.7 to 6.1	0.0	0.0 to 33.6
>0 to 50 Gy CRT	70	6.8	6.3 to 7.4	30.0	19.3 to 40.7	30	7.5	6.5 to 8.5	36.7	19.5 to 53.9	14	6.6	5.2 to 7.9	14.3	1.8 to 42.8
>50 Gy CRT	190	7.7	7.3 to 8.0	37.4	30.5 to 44.3	117	7.6	7.2 to 8.0	33.3	24.8 to 41.8	29	7.3	6.5 to 8.0	24.1	10.3 to 43.5

* PNET = primitive neuroectodermal tumor; CI = confidence interval; CRT = cranial radiotherapy.

† %Impaired = percent of patients falling at or below the 10th percentile based on reference to sibling control subjects, which is the standard threshold used for clinical impairment.

‡ Cognitive domains taken from Childhood Cancer Survivor Study–Neurocognitive Questionnaire task efficiency, emotional regulation, organization, and memory factors, respectively.

Table 6. Sociodemographic outcomes in central nervous system tumor survivors by region-specific cranial radiotherapy dose*

RT exposure	Education below college graduate RR† (95% CI)	Unemployed RR† (95% CI)	Never married RR† (95% CI)	Income <$20 000 RR† (95% CI)	Uninsured RR† (95% CI)
Posterior fossa					
None (referent category)	1.0 (Referent)	1.0 (Referent)	1.0 (Referent)	1.0 (Referent)	1.0 (Referent)
<30 Gy	1.0 (0.8 to 1.3)	1.1 (0.6 to 1.8)	1.3 (1.1 to 1.6)	1.6 (0.8 to 3.2)	1.2 (0.5 to 2.8)
30–49 Gy	1.0 (0.8 to 1.3)	1.3 (0.8 to 2.4)	1.4 (1.2 to 1.6)	1.9 (1.0 to 3.8)	0.8 (0.3 to 2.1)
≥50 Gy	1.0 (0.8 to 1.3)	1.2 (0.7 to 1.9)	1.3 (1.1 to 1.6)	2.1 (1.1 to 4.0)	0.8 (0.3 to 1.9)
Temporal lobe					
None	1.0 (Referent)	1.0 (Referent)	1.0 (Referent)	1.0 (Referent)	1.0 (Referent)
<30 Gy	0.9 (0.7 to 1.2)	1.1 (0.7 to 1.9)	1.2 (0.9 to 1.4)	1.8 (0.9 to 3.4)	1.4 (0.6 to 3.2)
30–49 Gy	1.2 (0.9 to 1.5)	1.5 (1.0 to 2.4)	1.5 (1.2 to 1.8)	2.3 (1.3 to 4.3)	1.8 (0.8 to 3.9)
≥50 Gy	1.2 (1.0 to 1.5)	1.7 (1.1 to 2.6)	1.4 (1.1 to 1.7)	2.9 (1.7 to 5.0)	1.8 (1.0 to 3.5)
Frontal lobe					
None	1.0 (Referent)	1.0 (Referent)	1.0 (Referent)	1.0 (Referent)	1.0 (Referent)
<30 Gy	1.0 (0.8 to 1.2)	1.2 (0.7 to 2.3)	1.3 (1.1 to 1.5)	2.1 (1.0 to 4.5)	1.2 (0.5 to 2.8)
30–49 Gy	1.1 (0.8 to 1.4)	1.6 (0.9 to 3.0)	1.5 (1.3 to 1.8)	2.1 (1.0 to 4.7)	0.8 (0.3 to 2.1)
≥50 Gy	1.2 (0.9 to 1.6)	2.1 (1.1 to 4.1)	1.5 (1.3 to 1.8)	1.8 (0.8 to 4.4)	0.8 (0.3 to 1.9)
Occipital lobe					
None	1.0 (Referent)	1.0 (Referent)	1.0 (Referent)	1.0 (Referent)	1.0 (Referent)
<30 Gy	0.9 (0.8 to 1.2)	1.1 (0.6 to 1.9)	1.3 (1.1 to 1.5)	1.9 (0.9 to 3.8)	1.3 (0.6 to 3.2)
30–49 Gy	0.9 (0.8 to 1.2)	1.2 (0.7 to 2.2)	1.5 (1.3 to 1.7)	2.0 (0.9 to 4.2)	1.0 (0.4 to 2.6)
≥50 Gy	1.0 (0.8 to 1.3)	1.5 (0.8 to 2.7)	1.5 (1.3 to 1.7)	1.6 (0.7 to 3.5)	1.1 (0.4 to 3.0)

* RR = relative risk; CI = confidence interval.

† Log-binomial generalized linear models adjusted for sex, age at diagnosis, and maximum radiation dose to any other segment.

between frontal and temporal lobe radiation and outcomes in employment and marriage. Because the frontal and temporal lobes mediate executive function and memory, these findings have biologically significant implications and underline the need to limit the extent of radiation fields during radiation delivery.

Some limitations of this research should be considered when assessing the validity and generalizability of these findings. First, medical conditions and sociodemographic and health status outcomes were self-reported. Subsequent neoplasms may be underreported despite a thorough validation process (5). Second, not all eligible survivors participated, and this could introduce participation bias, although previous assessment showed few differences between participants and nonparticipants (21). Third, in diagnosing the eligible cohort for this period, World Health Organization classifications of brain tumors were followed, according to which many glial tumors were classified "Astrocytoma, NOS," (not otherwise specified) precluding a more specific classification. Given the extremely poor overall survival of patients with high-grade gliomas in this study period, most 5-year survivors of glial tumors likely had low-grade lesions. Finally, primary therapeutic modalities have changed substantially since the period (1970–1986) when the patients in this study were initially treated: There has been a reduction in radiotherapy doses for lower risk patients, increased use of chemotherapy, including high-dose chemotherapy, and adoption of improved surgical and radiotherapy delivery techniques. Thus, the results of this analysis may not be generalizable to tomorrow's long-term survivors.

In conclusion, adult survivors of childhood CNS tumors are at high risk for late mortality and for developing second neoplasms and new chronic medical conditions related to their disease and treatment. Continued follow-up will help determine temporal patterns in incidence and late effects as this cohort ages. We are expanding the CCSS cohort to include 5-year survivors diagnosed from 1987 to 1999. Modern therapeutic regimens that increasingly use chemotherapy to reduce RT dose or use limited RT fields will likely improve long-term outcomes and minimize the risk of adverse late effects. Meanwhile, the dissemination of these results to care providers will enable informed medical care and help develop screening recommendations for patients.

References

1. Ries L, Eisner MP, Kosary CL. *SEER Cancer Statistics Review, 1975–2002.* Bethesda, MD: National Cancer Institute; 2005.
2. Mertens AC, Yasui Y, Neglia JP, et al. Late mortality experience in five-year survivors of childhood and adolescent cancer: the Childhood Cancer Survivor Study. *J Clin Oncol.* 2001;19(13):3163–3172.
3. Taylor DD, Potish RA. Late deaths following radiotherapy for pediatric tumors. *Am J Clin Oncol.* 1985;8(6):472–476.
4. Dama E, Pastore G, Mosso ML, et al. Late deaths among five-year survivors of childhood cancer. A population-based study in Piedmont Region, Italy. *Haematologica.* 2006;91(8):1084–1091.
5. Neglia JP, Friedman DL, Yasui Y, et al. Second malignant neoplasms in five-year survivors of childhood cancer: Childhood Cancer Survivor Study. *J Natl Cancer Inst.* 2001;93(8):618–629.
6. Broniscer A, Ke W, Fuller CE, Wu J, Gajjar A, Kun LE. Second neoplasms in pediatric patients with primary central nervous system tumors: the St. Jude Children's Research Hospital experience. *Cancer.* 2004; 100(10):2246–2252.
7. Cardous-Ubbink MC, Heinen RC, Bakker PJ, et al. Risk of second malignancies in long-term survivors of childhood cancer. *Eur J Cancer.* 2007; 43(2):351–362.
8. Duffner PK, Krischer JP, Horowitz ME, et al. Second malignancies in young children with primary brain tumors following treatment with prolonged postoperative chemotherapy and delayed irradiation: a Pediatric Oncology Group study. *Ann Neurol.* 1998;44(3):313–316.

9. Devarahally SR, Severson RK, Chuba P, Thomas R, Bhambhani K, Hamre MR. Second malignant neoplasms after primary central nervous system malignancies of childhood and adolescence. *Pediatr Hematol Oncol.* 2003;20(8):617–625.
10. Peterson KM, Shao C, McCarter R, MacDonald TJ, Byrne J. An analysis of SEER data of increasing risk of secondary malignant neoplasms among long-term survivors of childhood brain tumors. *Pediatr Blood Cancer.* 2006;47(1):83–88.
11. Jenkinson HC, Hawkins MM, Stiller CA, Winter DL, Marsden HB, Stevens MC. Long-term population-based risks of second malignant neoplasms after childhood cancer in Britain. *Br J Cancer.* 2004;91(11):1905–1910.
12. Hammal DM, Bell CL, Craft AW, Parker L. Second primary tumors in children and young adults in the North of England (1968–99). *Pediatr Blood Cancer.* 2005;45(2):155–161.
13. Oeffinger KC, Mertens AC, Sklar CA, et al. Chronic health conditions in adult survivors of childhood cancer. *N Engl J Med.* 2006;355(15):1572–1582.
14. Packer RJ, Gurney JG, Punyko JA, et al. Long-term neurologic and neurosensory sequelae in adult survivors of a childhood brain tumor: Childhood Cancer Survivor Study. *J Clin Oncol.* 2003;21(17):3255–3261.
15. Gurney JG, Kadan-Lottick NS, Packer RJ, et al. Endocrine and cardiovascular late effects among adult survivors of childhood brain tumors: Childhood Cancer Survivor Study. *Cancer.* 2003;97(3):663–673.
16. Palmer SL, Gajjar A, Reddick WE, et al. Predicting intellectual outcome among children treated with 35–40 Gy craniospinal irradiation for medulloblastoma. *Neuropsychology.* 2003;17(4):548–555.
17. Mulhern RK, Kepner JL, Thomas PR, Armstrong FD, Friedman HS, Kun LE. Neuropsychologic functioning of survivors of childhood medulloblastoma randomized to receive conventional or reduced-dose craniospinal irradiation: a Pediatric Oncology Group study. *J Clin Oncol.* 1998;16(5):1723–1728.
18. Gurney JG, Ness KK, Stovall M, et al. Final height and body mass index among adult survivors of childhood brain cancer: Childhood Cancer Survivor Study. *J Clin Endocrinol Metab.* 2003;88(10):4731–4739.
19. Zebrack BJ, Gurney JG, Oeffinger K, et al. Psychological outcomes in long-term survivors of childhood brain cancer: a report from the Childhood Cancer Survivor Study. *J Clin Oncol.* 2004;22(6):999–1006.
20. Mertens AC, Liu Q, Neglia JP, et al. Cause-specific late mortality among 5-year survivors of childhood cancer: the Childhood Cancer Survivor Study. *J Natl Cancer Inst.* 2008;100(19):1368–1379.
21. Robison LL, Mertens AC, Boice JD, et al. Study design and cohort characteristics of the Childhood Cancer Survivor Study: a multi-institutional collaborative project. *Med Pediatr Oncol.* 2002;38(4):229–239.
22. Stovall M, Weathers R, Kasper C, et al. Dose reconstruction for therapeutic and diagnostic radiation exposures: use in epidemiological studies. *Radiat Res.* 2006;166(1, pt 2):141–157.
23. Percy C, Holten V, Muir C. *International Classification of Diseases for Oncology.* 2nd ed. Geneva, Switzerland: World Health Organization; 1990.
24. Mertens AC, Walls RS, Taylor L, et al. Characteristics of childhood cancer survivors predicted their successful tracing. *J Clin Epidemiol.* 2004; 57(9):933–944.
25. Krull KR, Gioia G, Ness KK, et al. Reliability and validity of the Childhood Cancer Survivor Study Neurocognitive Questionnaire. *Cancer.* 2008;113(8):2188–2197.
26. Efron B, Tibshirani RJ. *An Introduction to the Bootstrap.* London, UK: Chapman & Hall/CRC; 1993.
27. Gray R. A class of K-sample tests for comparing the cumulative incidence of a competing risk. *Ann Stat.* 1988;16(3):1141–1154.
28. Gooley TA, Leisenring W, Crowley J, Storer BE. Estimation of failure probabilities in the presence of competing risks: new representations of old estimators. *Stat Med.* 1999;18(6):695–706.
29. Surveillance, Epidemiology, and End Results (SEER) Program. SEER*Stat Database: Incidence—SEER 9 Regs Limited-Use, November 2007 submission (1973–2005)—Katrina/Rita Population Adjustment—Linked to County Attributes—Total U.S., 1969–2005 Counties. National Cancer Institute: DCCPS, Surveillance Research Program, Cancer Statistics Branch; 2008. http://www.seer.cancer.gov/.
30. Wacholder S. Binomial regression in GLIM: estimating risk ratios and risk differences. *Am J Epidemiol.* 1986;123(1):174–184.
31. Liang KY, Zeger SL. Longitudinal data analysis using generalized linear models. *Biometrika.* 1986;73(1):13–22.
32. Royall R. Model robust confidence intervals using maximum likelihood estimators. *Int Stat Rev.* 1986;54(2):221–226.
33. Moore DM, GP. *Introduction to the Practice of Statistics.* 3rd ed. New York, NY: WH Freeman & Co; 1999:586–601.
34. Skov T, Deddens J, Petersen MR, Endahl L. Prevalence proportion ratios: estimation and hypothesis testing. *Int J Epidemiol.* 1998;27(1):91–95.
35. Deddens JP, Petersen MR, Lei X. Estimation of prevalence ratios when PROC GENMOD does not converge. In: SUGI 28 Conference*; March 30–April 2, 2003.* Seattle, WA.
36. Mulrooney DA, Dover DC, Li S, et al. Twenty years of follow-up among survivors of childhood and young adult acute myeloid leukemia: a report from the Childhood Cancer Survivor Study. *Cancer.* 2008;112(9):2071–2079.
37. Bluhm EC, Ronckers C, Hayashi RJ, et al. Cause-specific mortality and second cancer incidence after non-Hodgkin lymphoma: a report from the Childhood Cancer Survivor Study. *Blood.* 2008;111(8):4014–4021.
38. Hawkins MM, Kingston JE, Kinnier Wilson LM. Late deaths after treatment for childhood cancer. *Arch Dis Child.* 1990;65(12):1356–1363.
39. Robertson CM, Hawkins MM, Kingston JE. Late deaths and survival after childhood cancer: implications for cure. *BMJ.* 1994;309(6948):162–166.
40. Morris EB, Gajjar A, Okuma JO, et al. Survival and late mortality in long-term survivors of pediatric CNS tumors. *J Clin Oncol.* 2007;25(12):1532–1538.
41. MacArthur AC, Spinelli JJ, Rogers PC, Goddard KJ, Abanto ZU, McBride ML. Mortality among 5-year survivors of cancer diagnosed during childhood or adolescence in British Columbia, Canada. *Pediatr Blood Cancer.* 2007;48(4):460–467.
42. Fisher PG, Tihan T, Goldthwaite PT, et al. Outcome analysis of childhood low-grade astrocytomas. *Pediatr Blood Cancer.* 2008;51(2):245–250.
43. Anderson NE. Late complications in childhood central nervous system tumour survivors. *Curr Opin Neurol.* 2003;16(6):677–683.
44. Oeffinger KC, Mertens AC, Hudson MM, et al. Health care of young adult survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. *Ann Fam Med.* 2004;2(1):61–70.
45. Nathan PC, Greenberg ML, Ness KK, et al. Medical care in long-term survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. *J Clin Oncol.* 2008;26(27):4401–4409.
46. Landier W, Bhatia S, Eshelman DA, et al. Development of risk-based guidelines for pediatric cancer survivors: the Children's Oncology Group Long-Term Follow-Up Guidelines from the Children's Oncology Group Late Effects Committee and Nursing Discipline. *J Clin Oncol.* 2004; 22(24):4979–4990.
47. Hays DM, Landsverk J, Sallan SE, et al. Educational, occupational, and insurance status of childhood cancer survivors in their fourth and fifth decades of life. *J Clin Oncol.* 1992;10(9):1397–1406.
48. Foreman NK, Faestel PM, Pearson J, et al. Health status in 52 long-term survivors of pediatric brain tumors. *J Neurooncol.* 1999;41(1):47–53.
49. Cardarelli C, Cereda C, Masiero L, et al. Evaluation of health status and health-related quality of life in a cohort of Italian children following treatment for a primary brain tumor. *Pediatr Blood Cancer.* 2006;46(5): 637–644.
50. Carpentieri SC, Meyer EA, Delaney BL, et al. Psychosocial and behavioral functioning among pediatric brain tumor survivors. *J Neurooncol.* 2003;63(3):279–287.
51. Jenkin D, Danjoux C, Greenberg M. Subsequent quality of life for children irradiated for a brain tumor before age four years. *Med Pediatr Oncol.* 1998;31(6):506–511.
52. Speechley KN, Barrera M, Shaw AK, Morrison HI, Maunsell E. Health-related quality of life among child and adolescent survivors of childhood cancer. *J Clin Oncol.* 2006;24(16):2536–2543.
53. Heimans JJ, Taphoorn MJ. Impact of brain tumour treatment on quality of life. *J Neurol.* 2002;249(8):955–960.
54. Mostow EN, Byrne J, Connelly RR, Mulvihill JJ. Quality of life in long-term survivors of CNS tumors of childhood and adolescence. *J Clin Oncol.* 1991;9(4):592–599.
55. Hudson MM, Mertens AC, Yasui Y, et al. Health status of adult long-term survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. *JAMA.* 2003;290(12):1583–1592.

56. Mitby PA, Robison LL, Whitton JA, et al. Utilization of special education services and educational attainment among long-term survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. *Cancer*. 2003;97(4):1115–1126.
57. Zebrack BJ, Zevon MA, Turk N, et al. Psychological distress in long-term survivors of solid tumors diagnosed in childhood: a report from the Childhood Cancer Survivor Study. *Pediatr Blood Cancer*. 2007;49(1): 47–51.

Funding

National Cancer Institute (U24-CA55727 to L.L.R., Principal Investigator) and the American Lebanese-Syrian Associated Charities.

Note

Manuscript received November 24, 2008; revised April 7, 2009; accepted May 1, 2009.